



## ENVIRONMENTAL PROTECTION AGENCY

### 40 CFR Part 180

[EPA-HQ-OPP-2022-0932; FRL-10947-01-OCSP]

### **Ledprona (CAS# 2433753-68-3) for Use in or on Potato; Temporary Exemption from the Requirement of a Tolerance**

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final rule.

**SUMMARY:** This regulation establishes a temporary exemption from the requirement of a tolerance for residues of Ledprona (CAS# 2433753-68-3) in or on potatoes when used in accordance with the terms of Experimental Use Permit (EUP) No. 94614-EUP-1. GreenLight Bioscience, Inc. submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA) for a temporary exemption from the requirement of a tolerance for residues of Ledprona on all raw agricultural products and food products. After reviewing the petition and supporting data, the Agency has limited the temporary tolerance exemption to residues of Ledprona on potatoes only. This regulation eliminates the need to establish a maximum permissible level for residues of Ledprona in or on potatoes. This temporary tolerance exemption expires on April 30, 2025.

**DATES:** This regulation is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Objections and requests for hearings must be received on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

**ADDRESSES:** The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-20-2022-0932, is available at <https://www.regulations.gov> or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency

Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room, and the telephone number for the OPP Docket is (202) 566-1744 . Please review the visitor instructions and additional information about the docket available at <https://www.epa.gov/dockets>.

**FOR FURTHER INFORMATION CONTACT:** Frank Ellis, Biopesticides and Pollution Prevention Division (7511M), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; main telephone number: (703) 328-3074; email address: [BPPDFRNotices@epa.gov](mailto:BPPDFRNotices@epa.gov).

## **SUPPLEMENTARY INFORMATION:**

### **I. General Information**

#### *A. Does this action apply to me?*

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

#### *B. How can I get electronic access to other related information?*

You may access a frequently updated electronic version of 40 CFR part 180 through the Office of the *Federal Register*'s e-CFR site at <https://www.ecfr.gov/current/title-40>.

#### *C. How can I file an objection or hearing request?*

Under FFDCA section 408(g), 21 U.S.C. 346a(g), any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2022-0932 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-20-2022-0932, by one of the following methods:

- *Federal eRulemaking Portal*: <https://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be CBI or other information whose disclosure is restricted by statute.

- *Mail*: OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.

- *Hand Delivery*: To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <https://www.epa.gov/dockets/where-send-comments-epa-dockets>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <https://www.epa.gov/dockets>.

## **II. Background**

In the *Federal Register* of January 3, 2023 (88 FR 38) (FRL-9410-08-OCSPP), EPA issued a document pursuant to FFDCA section 408(d)(3), 21 U.S.C. 346a(d)(3), announcing the filing of a pesticide tolerance petition (2G9024) by GreenLight Bioscience, Inc., 200 Boston Ave., Suite 1000, Medford, MA 02155. The petitioner requested that 40 CFR part 180 be amended by establishing a temporary exemption from the requirement of a tolerance for residues of Ledprona on all raw agricultural products and food products. That document referenced a summary of the petition prepared by the petitioner GreenLight Biosciences, Inc., which is available in the docket at <https://www.regulations.gov>. There were no comments received in response to the notice of filing.

Based upon review of the petition and associated data and in accordance with its authority under FFDCA section 408(d)(4)(A)(i) and (r), EPA is establishing a temporary exemption from the requirement of a tolerance for residues of Ledprona in or on potatoes only when used in accordance with the terms of Experimental Use Permit No. 94614-EUP-1. The EUP is authorized for testing on potatoes only; therefore, the Agency has limited the temporary tolerance to potatoes alone.

### **III. Final Rule**

#### *A. EPA's Safety Determination*

Section 408(r) of FFDCA authorizes EPA to establish a temporary exemption from the requirement of a tolerance for residues covered by an experimental use permit issued under the Federal Insecticide, Fungicide, and Rodenticide Act. That section states that the provisions of section 408(c)(2) of FFDCA apply to exemptions issued under FFDCA section 408(r). Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the exemption is “safe.” Section 408(c)(2)(A)(ii) of FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which

there is reliable information.” This includes exposure through drinking water and in residential settings but does not include occupational exposure. Pursuant to FFDCA section 408(c)(2)(B), in establishing or maintaining in effect an exemption from the requirement of a tolerance, EPA must take into account the factors set forth in FFDCA section 408(b)(2)(C), which require EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance or tolerance exemption and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue . . . .” Additionally, FFDCA section 408(b)(2)(D) requires that EPA consider “available information concerning the cumulative effects of [a particular pesticide’s] . . . residues and other substances that have a common mechanism of toxicity.”

EPA evaluated the available toxicity and exposure data for Ledprona and considered its validity, completeness, and reliability, as well as the relationship of this information to human risk. In summary, dietary risk from the use of Ledprona is considered negligible because dietary exposure to residues of Ledprona in or on food or feed is expected to be negligible and no adverse effects were observed in toxicity testing. A full summary of the data upon which EPA relied and its risk assessments based on that data can be found within the document entitled, “Human health and product characterization for the Experimental Use Permit application for Calantha™, containing 0.8% of the new active ingredient ‘Ledprona’ dsRNA for use on potatoes and associated petition to establish a temporary tolerance exemption” (Human Health Risk Assessment). This document, as well as other relevant information, is available in the docket for this action as described under **ADDRESSES**.

Available data have demonstrated that, with regard to humans, Ledprona presents no adverse effects of concern and exposure to the active ingredient will be insignificant. Ledprona consists of double-stranded ribonucleic acid (dsRNA) that induces mortality of the Colorado potato beetle (*Leptinotarsa decemlineata*) via a gene silencing mode of action. When dsRNA is applied, it causes the inhibition (or silencing) of the gene product, messenger RNA (mRNA),

preventing the translation of the mRNA to proteins. Ledprona dsRNA targets the *Proteasome subunit beta type-5 (PSMB5)* mRNA sequence in the Colorado potato beetle. *PSMB5* mRNA encodes a protein that regulates proper folding of other proteins in the Colorado potato beetle. Once Ledprona is ingested by the Colorado potato beetle, over time the lack of *PSMB5* mRNA leads to the reduction of the *PSMB5* protein and ultimately causes mortality.

Dietary exposure to Ledprona through residues of the active ingredient in or on food or feed as well as in drinking water is expected to be negligible. As detailed in the Human Health Risk Assessment, dietary exposure to Ledprona is anticipated to be limited for the following reasons: (1) The EUP is limited to foliar application on potatoes. Underground tubers would not be directly exposed to Ledprona, so consumption of residues on potatoes is expected to be limited; (2) Once applied, Ledprona is expected to undergo rapid degradation due to microbial activity; (3) Submitted data show that Ledprona rapidly degrades in the mammalian gut; and (4) Mammals possess physiological barriers (*i.e.*, nucleases in saliva and gastrointestinal tract, acidic conditions in the stomach, presence of multiple membrane barriers) that prevent uptake of dsRNA. Ledprona is expected to degrade within 20-25 hours after application at the EUP label rates in microbially rich environments (*e.g.*, soil). Further, Ledprona rapidly degrades in simulated gastric fluids (within 10 minutes in simulated intestinal fluid and within 20 minutes in simulated gastric fluid) and degrades at similar rates as RNA extracted from plants. This information allows EPA to rely on a well-established history of exposure to RNA molecules via food. These data indicate that dietary exposure from the use of this active ingredient is considered negligible.

In addition to the lack of exposure described above, submitted acute oral toxicity studies demonstrated a lack of hazard of Ledprona to the mammalian surrogate species, rats, *in vivo*. A bioinformatic analysis was conducted to evaluate the likelihood of off-target effects of the Ledprona dsRNA in humans *in silico*, by computer analysis of Ledprona RNA segments. The analysis represents the potential for Ledprona dsRNA 21-mers (21 nucleotide segments) to

match RNA segments in the human transcriptome (*i.e.*, the set of all human RNA transcripts, including coding and non-coding). The analysis identified three Ledprona 21-mers which display the potential to match and subsequently silence target mRNAs *in silico*. The three 21-mers are predicted to overlap with non-coding RNAs. However, the analysis assumes that the 21-mers identified would be capable of bypassing physiological barriers to access the cell nucleus in sufficient quantities. As described above, submitted data show that Ledprona rapidly degrades in the mammalian gut, and the physiological barriers present in mammals (*i.e.*, nucleases in saliva and gastrointestinal tract, acidic conditions in the stomach, presence of multiple membrane barriers) impede the uptake of dsRNA, therefore negating any silencing potential of the 21-mer partial matches via the oral route of exposure.

The potential for residential exposure is highly unlikely because there are no residential uses proposed for the EUP under which Ledprona would be applied. Non-occupational exposure is unlikely because applications will occur in experimental plots generally not accessible to bystanders. However, should bystander exposure occur post-application (*i.e.*, contact with treated foliage), adverse effects are not expected since Ledprona is non-toxic through the dermal route of exposure.

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.” No risk of cumulative toxicity/effects from Ledprona have been identified as no toxicity has been shown for Ledprona in the submitted studies. Therefore, EPA has not assumed that Ledprona has a common mechanism of toxicity with other substances.

Although FFDCA section 408(b)(2)(C) provides for an additional tenfold margin of safety for infants and children in the case of threshold effects, EPA has determined that there are no such effects due to the lack of toxicity of Ledprona. As a result, an additional margin of safety for the protection of infants and children is unnecessary.

Based upon its evaluation, EPA concludes that there is reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to residues of Ledprona in or on potatoes. This includes all anticipated dietary exposures for which there is reliable information. The Agency has arrived at this conclusion based on the rapid degradation of the active ingredient in environmental and biological conditions, mammalian physiological barriers limiting the uptake of dsRNA, and the lack of effects observed in toxicity testing.

#### *B. Analytical Enforcement Methodology*

EPA has determined that an analytical method is not required for enforcement purposes since the Agency is establishing an exemption from the requirement of a tolerance without any numerical limitation.

#### *C. Conclusion*

Based upon its evaluation in the Human Health Risk Assessment, EPA concludes that there is a reasonable certainty that no harm will result to the U.S. population, including infants and children, from aggregate exposure to residues of Ledprona in or on potatoes. Therefore, a temporary exemption from the requirement of a tolerance is established for residues of Ledprona in or on potatoes when used in accordance with the terms of Experimental Use Permit No. 94614-EUP-1.

### **IV. Statutory and Executive Order Reviews**

This action establishes a tolerance exemption under FFDCA section 408(d) in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled “Regulatory Planning and Review” (58 FR 51735, October 4, 1993). Because this action has been exempted from review under Executive Order 12866, this action is not subject to Executive Order 13211, entitled “Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use” (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled “Protection of



Children from Environmental Health Risks and Safety Risks” (62 FR 19885, April 23, 1997).

This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), nor does it require any special considerations under Executive Order 12898, entitled “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations” (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the exemption in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), do not apply.

This action directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this action. In addition, this action does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note).

## **V. Congressional Review Act**

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the *Federal Register*. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

**List of Subjects in 40 CFR Part 180**

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: May 1, 2023.

**Frank Ellis,**  
*Acting Director,*  
*Biopesticides and Pollution Prevention Division,*  
*Office of Pesticide Programs.*

Therefore, for the reasons stated in the preamble, EPA is amending 40 CFR part 180 as follows:

**PART 180—TOLERANCES AND EXEMPTIONS FOR PESTICIDE CHEMICAL  
RESIDUES IN FOOD**

1. The authority citation for part 180 continues to read as follows:

**Authority:** 21 U.S.C. 321(q), 346a and 371.

2. Add §180.1403 to subpart D to read as follows:

**§ 180.1403 Ledprona; temporary exemption from the requirement of a tolerance.**

A temporary exemption from the requirement of a tolerance is established for residues of Ledprona in or on potato when used in accordance with the terms of Experimental Use Permit No. 94614-EUP-1. This temporary exemption from the requirement of a tolerance expires on April 30, 2025.

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